(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 July 2004 (15.07.2004)

PCT

(10) International Publication Number
WO 2004/058235 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number:
PCT/US2003/040174

(22) International Filing Date:
16 December 2003 (16.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/433,685 16 December 2002 (16.12.2002) US
60/460,206 2 April 2003 (02.04.2003) US

(71) Applicant *(for all designated States except BB, US)*: TEVA PHARMACEUTICAL INDUSTRIES LTD. [IL/IL]; 5 Basel Street, P.O. Box 1390, 49131 Petah Tiqva (IL).

(71) Applicant *(for BB only)*: TEVA PHARMACEUTICALS USA, INC. [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: FLASHNER-BARAK, Moshe [IL/IL]; Hefetz Mordechai 15, Petach Tiqva (IL). LERNER, Itzhak, E. [IL/IL]; Wolfson 32, Petach Tikva (IL). ROSENBERGER, Vered [/IL]; Ms. Landau 3, Givat Masuah, Jerusalem (IL).

(74) Agents: BRAINARD, Charles, R. et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004-1050 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/058235 A2

(54) Title: METHOD OF INCREASING BIOAVAILABILITY OF ALENDRONATE OR OTHER BIS-PHOSPHONATE BY PREDOSE ADMINISTRATION OF VITAMIN D DERIVATIVE

(57) Abstract: The present invention provides a method of increasing the bioavailability of a bis-phosphonate comprising administering an effective predose of a vitamin D derivative, such as alphacalcidol or calcitriol, and after a time interval, administering a therapeutic dose of bis-phosphonate, such as alendronate. The present invention also relates to the use of vitamin D derivatives and bisphosphonates for the manufacture of medicaments for treating osteoporosis, metastatic bone disease, and Paget's disease.

METHOD OF INCREASING BIOAVAILABILITY OF ALENDRONATE OR OTHER BIS-PHOSPHONATE BY PREDOSE ADMINISTRATION OF VITAMIN D DERIVATIVE

This application claims the benefit of U.S. Provisional Patent Applications Serial Nos. 60/433,685 filed December 16, 2002, and 60/460,206, filed April 2, 2003, both of which are incorporated herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to a method of increasing the bioavailability of bis-phosphonates such as alendronate by administering to the recipient a predose of alphacalcidol (1α-hydroxyvitamin D_3) at least six hours before the administration of the therapeutic dose of the bis-phosphonate.

The present invention relates to a method of increasing the bioavailability of bis-phosphonates such as alendronate by administering to the recipient a predose of calcitriol (1α,25-dihydroxyvitamin D_3) in which the calcitriol is delayed from immediate release at least about three to about five hours after administration, and administering a therapeutic dose of the bis-phosphonate at least about six hours after administration of the calcitriol predose.

BACKGROUND OF THE INVENTION

Treatment of osteoporosis, metastatic bone disease, and Paget's disease can benefit from improvements in controlled gastric release and multiple dose delivery technology. Bis-phosphonates such as sodium alendronate, risedronate, etidronate, zoledronic acid and tiludronate are commonly prescribed drugs for treatment of these diseases. Despite their benefits, bis-phosphonates suffer from very poor oral bioavailability. Alendronate has less than 1% bioavailability. Gert, B. J., Holland, S.D., Kline, W.F., Matuszewski, B. K., Freeman, A.,Quan, H., Lasseter, K. C., Mucklow, J. C., Porras, A. G. "Studies of The Oral Bioavailability of Alendronate," *Clinical Pharmacology & Therapeutics* **1995**, *58*, 288-298. Its absorption is inhibited by foods and beverages other than water. *Id.* Side effects experienced by patients who have taken alendronate include irritation of the upper gastrointestinal mucosa. Liberman, U. A., Hirsch, L. J.; "Esophagitis and Alendronate" *N. Engl. J. Med.*, **1996**,

335, 1069-70. This irritation can lead to more serious conditions. *Physicians' Desk Reference*, Fosamax, Warnings.

Alendronate is best absorbed from the upper GI tract (duodenum and jejunum). Lin, J. H. "Bisphosphonates: A Review of Their Pharmacokinetic Properties," *Bone*, **1996**, *18*, 75-85; Porras, A. G., Holland, S. D., Gertz, B. J., "Pharmacokinetics of Alendronate," *Clin. Pharmacokinet* **1999**, *36*, 315-328. Alendronate is best absorbed at a pH of ~6. Gert, B. J., Holland, S.D., Kline, W.F., Matuszewski, B. K., Freeman, A., Quan, H., Lasseter, K. C., Mucklow, J. C., Porras, A. G. "Studies of The Oral Bioavailablity of Alendronate," *Clinical Pharmacology & Therapeutics*, **1995**, *58*, 288-298. As discussed in commonly-assigned U.S. Pat. No. 6,476,006, controlled gastric release of alendronate would allow for extended delivery of the drug to the duodenum and jejunum parts of the intestine and should result in improved bioavailability, and thus allow lower dosing and less irritation.

In addition to bis-phosphonate therapy, options in the treatment of osteoporosis include hormone replacement therapy and calcium supplementation therapy. Kleerekoper, M., Schein, J. R. "Comparative Safety of Bone Remodeling Agents with A Focus on Osteoporosis Therapies," *J. Clin. Pharmacol.* **2001**, *41*, 239. Increased calcium levels can potentially improve the state of bone mineralization in patients with osteoporosis. Over the last thirty years, calcium supplementation, along with vitamin D or vitamin D derivatives such as calcitriol, have been options for treating the problems of osteoporosis. Cannigia, A., Vattimo, A. "Effects of 1,25 Dihydroxycholecalciferol on Calcium Absorption in Postmenopausal Osteoporosis," *Clin. Endocrinol.*, **1979**, *11*, 99; Riggs, B. L., Nelson, K. L. "Effect of Long Term Treatment with Calcitriol on Calcium Absorption and Mineral Metabolism in Postmenopausal Osteoporosis, *J. Clin. Endocrinol. Metab.* **1985**, *61*, 457; Reid, I. R., Ames, R. W., Evans, M. C., Gamble, G. D., Sharpe, S. J. "Long Term Effects of Calcium Supplementation on Bone Loss and Fracture in Post-menopausal Women, a Randomized Controlled Trial, *Am. J. Med.*, **1995**, *98*, 331. Calcitriol (1,25-dihydroxyvitamin D_3) is a vitamin D derivative that is active in the regulation of the absorption of calcium from the gastrointestinal tract. *Physicians' Desk Reference*, Rocaltrol Oral Solution, Description. Calcitriol is the biologically active metabolite of vitamin D_3 and stimulates intestinal calcium transport. *Merck Index*, 13th Ed., 1643. Calcitriol is rapidly absorbed from the intestine and reaches peak serum concentrations within three to six hours after ingestion. *Physicians' Desk Reference*,

Rocaltrol Oral Solution, Pharmacokinetics. Calcitriol is used to treat calcium deficiency.

Over the past several years, successful trials have been performed that confirm that there is a synergistic effect in using a combined therapy of calcitriol and bis-phosphonates. Frediani, B., Allegri, A., Bisogno, S., Marcolongo, R. "Effects of Combined Treatment with Calcitriol Plus Alendronate on Bone Mass and Bone Turnover in Postmenopausal Osteoporosis-Two Years of Continuous Treatment," *Clin. Drug Invest.* **1998**, *15*, 223; Masud, T., Mulcahy, B., Thompson, A. V., Donnolly, S., Keen, R. W., Doyle, D. V., Spector, T. D., "Effects of Cyclical Etidronate Combined with Calcitriol Versus Cyclical Etidronate Alone on Spine and Femoral Neck Bone Mineral Density in Postmenopausal Women," *Ann. Rheum. Dis.*, **1998**, *57*, 346; Malvolta, M., Zanardi, M., Veronesi, M., Ripamonti C., Gnudi, S. "Calcitriol and Alendronate Combination Treatment in Menopausal Women with Low Bone Mass," *Int. J. Tissue React.* **1999**, *21*, 51; Nuti, R., Martini, G., Giovani, S., Valenti, R. "Effect of Treatment with Calcitriol Combined with Low-dosage Alendronate in Involutional Osteoporosis," *Clin. Drug Invest.*, **2000**, *19*, 56. The goal of the combined therapy trials is to improve therapeutic results and lower the dosage of the two drugs. In these trials the drugs were given separately and co-administered. International Publication WO 2001/028564 discloses a tablet containing a combination of calcitriol and alendronate in a particular range of ratios of the two drugs.

Although there has been a recognition of the benefits of combination therapy in the treatment of osteoporosis, metastatic bone disease and Paget's disease, and although there have been advances in controlled release systems for multi-dose medications, there remains a need for an improved controlled delivery system and an improved dosing regimen for a bis-phosphonate and a calcium transport stimulator in order to fully realize the advantages of combined therapy.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a method of increasing the bioavailability of a bis-phosphonate comprising administering an effective predose of a vitamin D derivative, especially calcitriol, alphacalcidol, 24,25-dihydroxy vitamin D_3, and calcifediol, and after a time interval, especially about 6 hours to about 14

hours, administering a therapeutic dose of bis-phosphonate, especially alendronate, risedronate, etidronate, zoledronate, and tiludronate.

In another aspect, the time interval is about equal to the amount of time required for blood calcium level to reach a maximum after administering the vitamin D derivative. The present method especially provides for the predose of a vitamin D derivative to be administered at bedtime and the dose of a bis-phosphonate to be administered before eating. The time interval is achieved by changing the time of administration of vitamin D derivative, changing the time of administration of bis-phosphonate, and by using delay-release technology known in the pharmaceutical art.

In another aspect, the present invention relates to the use of a bis-phosphonate for the manufacture of a medicament for treating osteoporosis, metastatic bone disease, and Paget's disease by administering an effective predose of a vitamin D derivative prior to administering the bis-phosphonate.

In another aspect, the present invention relates to the use of a vitamin D derivative for the manufacture of a medicament for treating osteoporosis, metastatic bone disease, and Paget's disease by administering a bis-phosphonate after administering the vitamin D derivative.

In yet another aspect, the present invention relates to the use of a vitamin D derivative and a bis-phosphonate for the manufacture of a medicament for treating osteoporosis, metastatic bone disease, and Paget's disease by administering the vitamin D derivative and then after a time interval administering the bis-phosphonate.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of combination drug therapy to increase the bioavailability of a bis-phosphonate that includes the steps of administering a predose of a calcium transport stimulator, especially alphacalcidol, followed by administration of a bis-phosphonate calcium resorption inhibitor at least about 6 hours after the calcium transport stimulator is administered. The present invention takes advantage of the fact that a calcium transport stimulator depletes the calcium concentration in the intestine, in addition to its recognized benefit of increasing calcium in the blood. Complexation of a bis-phosphonate with calcium in the gut inhibits its absorption. The depletion of calcium results in improved absorption of the bis-phosphonate in the intestine. When a bis-phosphonate calcium resorption inhibitor is delivered to the upper small intestine after delivery of a vitamin

D derivative that is a calcium transport stimulator, absorption of the bis-phosphonate will be increased. The bis-phosphonate will enter an environment partially depleted in calcium due to the transport activity of the vitamin D derivative. This depleted calcium environment will thus allow a higher absorption of the bis-phosphonate, thereby allowing a dose lowering in addition to the dose lowering caused by the synergistic effect of the bis-phosphonate and vitamin D derivatives that occurs after reaching the bloodstream.

In one embodiment, the present invention provides a method of increasing the bioavailability of a bis-phosphonate by administering an effective predose of a vitamin D derivative and, at least about 6 hours later, preferably about 6 hours to about 14 hours later, administering a therapeutic dose of a bis-phosphonate. In this embodiment, the preferred vitamin D derivative is alphacalcidol and the preferred bis-phosphonate is alendronate.

In another embodiment, the present invention provides a method of increasing the bioavailability of a bis-phosphonate by administering a delayed-release effective predose of a vitamin D derivative and, at least about 6 hours later, preferably about 6 hours to about 14 hours later, administering a therapeutic dose of a bis-phosphonate. Preferably, the release of the vitamin D derivative is delayed about 3 to about 5 hours after the vitamin D derivative is administered. In this embodiment, the preferred vitamin D derivative is calcitriol and the preferred bis-phosphonate is alendronate.

As used herein, bioavailability means "the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action;" "the fraction of drug absorbed as such into the systemic circulation." *Goodman and Gilman's The Pharmalogical Basis of Therapeutics* 5, 18 (Joel G. Hardman et. al. eds., McGraw Hill Pub. 10th ed. **2001**). Oral bioavailability can be estimated based on secondary information (e.g., urinary excretion or the amount of the drug excreted unchanged in the urine, expressed as a percentage of the administered dose). *Id.* at 1918.

The present invention includes the step of administering of an effective predose of a vitamin D derivative. The skilled artisan will understand that a predose is the dose of the vitamin D derivative that is administered before the administration of the therapeutic dose of the bis-phosphonate. An effective predose means that the calcium transport stimulator may be dosed in any amount that results in increased intestinal absorption of the bis-phosphonate compared to an equal dose of the bis-

phosphonate administered without the calcium transport stimulator. One example of an effective predose is a dose between about 0.1 μg and about 10 μg of a vitamin D derivative.

The vitamin D derivatives useful in the practice of the present invention are calcium transport stimulators. Calcium transport stimulators facilitate the intestinal absorption of calcium. *Id.* at 1728. Vitamin D derivatives useful in the practice of the present invention are structural analogs of the hormone, vitamin D. Examples of vitamin D derivatives useful in the practice of the present invention include calcitriol, alphacalcidol, 24,25-dihydroxy vitamin D_3, and calcifediol. In one embodiment, the preferred vitamin D derivative is alphacalcidol. A preferred dose range of alphacalcidol is about 0.1 μg to about 10 μg, more preferably between about 0.2 μg to about 2 μg. In another embodiment, the preferred vitamin D derivative is calcitriol. A preferred dose range of alphacalcidol is about 0.1 μg to about 10 μg, more preferably between about 0.2 μg to about 2 μg.

Alphacalcidol, or 1α-hydroxyvitamin D_3, is a synthetic analog of calcitriol, the hormonal form of Vitamin D_3. Alphacalcidol stimulates intestinal calcium absorption, the transport of calcium from the intestine to the bloodstream. When alphacalcidol enters the intestine, several hours must pass before blood calcium level peaks. In order to release the bis-phosphonate into an environment of minimum calcium, administration of the alphacalcidol predose should precede the administration of the bis-phosphonate dose by a time interval of several hours. A time interval of several hours, e.g. about 6 hours to about 14 hours, allows for maximum bioavailability of bis-phosphonate.

The maximum increase in bis-phosphonate bioavailability is observed when the time interval between administration of the alphacalcidol predose and the bis-phosphonate dose is at least about 6 hours, preferably about 6 hours to about 14 hours, more preferably about 6 hours to about 12 hours, and most preferably about 6 hours to about 10 hours. This time interval allows for a convenient dosage regimen in which the predose of alphacalcidol can be administered between 8 P.M. and midnight and the bis-phosphonate dose can be administered between 6 A.M. and 10 A.M. on the following morning, preferably before eating. This dosing method increases the bioavailability of bis-phosphonate.

Calcitriol exhibits a maximum effect at about 3 hours after administration. The present invention provides a method of improving the bis-phosphonate

bioavailability by predosing with calcitriol in a delayed-release delivery system. The present invention accommodates differences in calcium depleting characteristics of different vitamin D derivatives that are calcium transport stimulators by extending the time interval for maximum effect of the vitamin D derivative by delaying its release following administration of the vitamin D derivative predose. When the vitamin D derivative is calcitriol, the calcitriol dose is delayed between about three hours and about five hours by providing the calcitriol dosage form with an enteric coating known in the art, e.g., EUDRAGIT® L, EUDRAGIT® S, cellulose acetate phthalate. Such enteric coating materials are pH-sensitive and can withstand prolonged contact with acidic gastric fluids. Therefore, the enteric coating does not dissolve until after stomach passage but dissolves readily in the mildly acidic to neutral environment of the small intestine. The level of coating necessary to achieve the desired delay of onset of drug release can be readily determined by experimentation of one skilled in the art (*see*, e.g., *United States Pharmacopeia, 26th Rev./National Formulary, 21st Ed.*, 2002, <724> Drug Release, Delayed-Release (Enteric-Coated) Articles – General Drug Release Standard, 2160-2161; *Pharmaceutical Dosage Forms and Drug Delivery Systems*, H.C. Ansel, L.V. Allen, Jr., N.G. Popovich (Lippincott Williams & Wilkins, pub., 1999), Modified-Release Dosage Forms and Drug Delivery Systems, 223, 231-240).

Calcitriol, or 1α,25-dihydroxyvitamin D_3, is the primary active metabolite of Vitamin D. *Goodman and Gilman's The Pharmalogical Basis of Therapeutics, supra*, at 1727. Like alphacalcidol, calcitriol is reported to stimulate intestinal calcium absorption. For calcitriol, blood calcium level is reported to peak at about 3 hours to about 5 hours after calctriol enters the intestine. In order to release the bis-phosphonate into an environment of minimum calcium, administration of the calcitriol predose should precede the administration of the bis-phosphonate dose by a time interval of several hours that depends on the rate of intestinal calcium depletion. When the calcitriol is delayed from immediate release at least about 3 to about 5 hours after its administration, a time interval of several hours, e.g. about 6 hours to about 14 hours, allows for maximum bioavailability of bis-phosphonate.

In one embodiment using a delay-release calcitriol predose, the release of the calcitriol predose is delayed about 3 hours to about 5 hours after administering the predose. The time interval between delay-release calcitriol predose and bis-phosphonate dose is at least about 6 hours, preferably about 6 hours to about 14 hours,

more preferably about 6 hours to about 12 hours, and most preferably about 6 hours to about 10 hours. This embodiment provides for a convenient dosage regimen in which the calcitriol predose can be administered between 8 P.M. and midnight and the bis-phosphonate dose can be administered between 6 A.M. and 10 A.M. on the following morning, preferably before eating. This dosing method increases the bioavailability of bis-phosphonate. The convenience of this dosing method improves patient compliance.

The embodiments of the present invention include a time interval between the administration of the effective predose of vitamin D derivative and the administration of the therapeutic dose of bis-phosphonate. The time interval can be expressed as T = t2 –t1, where T is the time interval, t1 is the time at which the vitamin D derivative is administered, and t2 is the time at which the bis-phosphonate is administered. The time interval should be about equal to the amount of time required for blood calcium level to reach a maximum after administering the vitamin D derivative. By adjusting the time interval, one can release the bis-phosphonate into an environment of minimum calcium, thereby increasing the bioavailability of bis-phosphonate.

The present invention includes the step of administering a therapeutic dose of bis-phosphonate. A therapeutic dose of bis-phosphonate is an amount of bis-phosphonate that treats or ameliorates diseases including osteoporosis, metastatic bone disease, and Paget's disease, among others.

The bis-phosphonates useful in the practice of the present invention are calcium resorption inhibitors. Examples of bis-phosphonates useful in the practice of the present invention include alendronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "alendronate"), risedronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "risedronate"), etidronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "etidronate"), zoledronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "zoledronate"), and tiludronic acid and pharmaceutically acceptable salts thereof (hereinafter, collectively known as "tiludronate"). The skilled artisan will recognize that pharmaceutically acceptable salts can exist as solvates, e.g., hydrates. One skilled in the art would recognize that these bis-phosphonates can also be provided as esters. The bis-phosphonates may be provided in any pharmaceutically acceptable salt or acid form, salts being generally preferred because they cause less membrane

irritation. Alendronate is preferably provided as a monosodium salt monohydrate or trihydrate. Risedronate is preferably provided as a monosodium salt hemipentahydrate. Etidronate and tiludronate are preferably provided as hydrated or anhydrous disodium salts. Zoledronate is preferably provided as a disodium salt tetrahydrate or trisodium salt hydrate.

The most preferred bis-phosphonate of the present invention is alendronate. The preferred therapeutic dose of alendronate is between about 1 mg and about 100 mg, most preferably between about 10 mg and about 70 mg.

Administration of the vitamin D derivative in the combination drug regiment can be by any means known in the art. Solid oral dosage forms are preferred.

Administration of the bis-phosphonate in the combination drug regimen can also be by any means known in the art. Administration *via* a solid oral dosage form is preferred. The solid oral dosage form can be of the conventional type well known in the art (e.g. Fosamax®).

The bis-phosphonates and vitamin D derivatives useful in the practice of the present invention can be manufactured into medicaments that include one or more excipients known in the art. Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

Diluents increase the bulk of a solid pharmaceutical product and may make it easier for the patient and care giver to handle. Diluents include, for example, microcrystalline cellulose (*e.g.*, Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (*e.g.*, Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Compacted dosage forms like those of the present invention may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include, but are not limited to, acacia, alginic acid, carbomer (*e.g.*, carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, glucose, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (*e.g.*, Klucel®), hydroxypropyl methylcellulose (HPMC) (*e.g.*, Methocel®), liquid glucose,

magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, polyvinylpyrrolidone (*e.g.*, Kollidon®, Plasdone®), starch, pregelatinized starch, sodium alginate and alginate derivatives.

The dissolution rate of a compacted dosage form in the patient's stomach also may be adjusted by the addition of a disintegrant or second superdistegrant to the dosage form, in addition to the superdisintegrant of the present inventive composition. Such additional disintegrants include, but are not limited to, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium (*e.g.*, Ac-Di-Sol®, Primellose®), crospovidone (*e.g.*, Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (*e.g.*, Explotab®) and starch.

Glidants can be added to improve the flow properties of a solid composition and improve the accuracy of dosing. Excipients that may function as glidants include, but are not limited to, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by compaction, a composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease release of the product from the dye. Lubricants include, but are not limited to, magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, surfactants, talc, waxes and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the dosage forms of the present invention include, but are not limited to, maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid ethyl maltol, and tartaric acid.

The dosage forms may also be colored using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

The dosage form may be prepared conventionally by dry blending, dry granulation or wet granulation of the active ingredients and any other desired excipients.

In a dry granulation, the active ingredients and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may be compressed subsequently into a final dosage form. It will be appreciated that the processes of slugging or roller compaction, followed by comminution and recompression render the hydrogel, superdisintegrant, tannic acid, and active ingredients intragranular in the final dosage form. Alternatively, any of the active ingredients or excipients may be added after comminution of the compacted composition, which results in that active ingredient or excipient being extragranular.

As an alternative to dry granulation, the blended composition may be compressed directly into the final pharmaceutical dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Thus, the active ingredients and any other desired excipients are blended with the composition prior to direct compression tableting. Such additional excipients that are particularly well suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate, and colloidal silica.

An additional alternative to dry granulation is wet granulation. The blend of excipients may be granulated using an alcohol or water and alcohol mixture as a granulation solvent by standard granulation techniques known in the art followed by drying, sieving, milling and compressing into the final dosage form.

The active ingredients may be compacted using conventional compression techniques.

Having thus described the invention with reference to certain preferred embodiments, it is further illustrated by the following non-limiting examples.

EXAMPLES

EXAMPLE 1: In-Vivo Study on Improving the Bioavailability of Alendronate: Effect of Varying Predose Intervals of Alphacalcidol in a Combination Drug Regimen with Alendronate.

An *in vivo* study in an animal model was conducted to determine whether alphacalcidol, administered in varying predose intervals (time intervals) in combination therapy with alendronate increased the bioavailability of alendronate compared with the administration of alendronate alone.

Six female beagle dogs, each approximately 2 years old and weighing approximately 9 kg were the animal models in this study. The same animals were used in each of five separate treatment sessions lasting 34-42 hours each, the duration of each session depending on the predose test interval being measured. The same drugs at identical dosages were administered in every treatment, *viz.*, alphacalcidol (ALPHA D3®, 1.0 μg gel capsule; TEVA) was the Vitamin D_3 derivative administered as the predose drug and alendronate sodium (Fosalan®, 10 mg tablet, Merck, Sharp & Dohme) was the bis-phosphonate administered as the therapeutic drug. There was a 7 day wash-out period between sessions. The clinical state of each dog was checked within 48 hours prior to each treatment session and again after the last session. In each session the animals were dosed in the fasted state (n.p.o. 10-12 hours). The dogs were fed a standardized meal (canned Bonzo meat, 1 full can, 425 grams) four hours after administration of the therapeutic dose of alendronate.

During each session, the dogs were housed in steel metabolic cages. Urine samples were recovered from the bottom of the metabolic cages. At each collection point, two representative samples of urine (*ca.* 5 ml each) were taken in capped polypropylene vials and immediately frozen at -20° C. The remainder of the sample was frozen and retained.

Urine samples were analyzed for alendronate by high performance liquid chromatography (HPLC) with fluorescence detection (Anapharm, Inc., Quebec, Canada).

In each session, the predose study drug, alphacalcidol, was administered in the A.M., in the fasted state, with 10-20 ml tap water to facilitate swallowing. During the monitoring (collection) period of each session, dogs were hydrated *via* gastroesophageal tube with 300 ml tap water on the evening prior to initiation of each

testing session and subsequently, with 150 ml tap water every two hours post-administration of the therapeutic dose of alendronate, for up to 10 hours. As noted above, a meal was allowed 4 hours after the administration of alendronate.

In the first (reference) study session, the predose of alphacalcidol and the therapeutic dose of alendronate were administered simultaneously, with 10-20 ml tap water to facilitate swallowing, immediately followed by 250 ml tap water *via* a gastroesophageal tube.

In the second through fifth study sessions, the predose of alphacalcidol was administered with 10-20 ml tap water. At intervals of 1, 2, 3, or 6 hours, respectively, following the administration of the predose of alphacalcidol in each of the consecutive study sessions, the therapeutic dose of alendronate was administered with 10-20 ml tap water, immediately followed by 250 ml tap water *via* gastroesophageal tube.

For each alphacalcidol predose time interval tested, cumulative levels of alendronate concentrations in urine were determined over 24 hours post-administration of the therapeutic alendronate dose at collection time points beginning at the 0 hour prior to alendronate dose and again at 3, 6, 9, and 24 hours following the alendronate dose.

The results of the analyses of alendronate in urine for the five treatments are reported in Tables 1A–1E, 2 and 3. Tables 1A–1E give the results of the excretion of alendronate into dog urine for each of the experimental sessions. Table 2 collects the average of the total excreted alendronate as a function of the time interval between alphacalcidol administration and alendronate administration. Table 3 gives the average of total excreted alendronate as a function of the time interval between calcitriol administration and alendronate administration carried out in a separate experiment.

The results showed that the total alendronate bioavailability increased considerably 6 hours after the administration of alphacalcidol. It is expected that this increase will continue to be found when the time interval between administration of the predose of alphacalcidol and the subsequent administration of the therapeutic dose of alendronate is increased to 8, 10 or 12 hours. Alendronate bioavailability without the vitamin D derivative in this dog model was about 30 μg to 50 μg. Calcitriol, administered 3 hours before the alendronate administration increased this value to 108 μg. The improvement in alendronate bioavailability was similar for the two vitamin

D derivatives, calcitriol and alphacalcidol, but the optimal time interval between administration of the predose and maximum alendronate bioavailability was delayed in the case of alphacalcidol. This delay can be used to advantage in designing a combination drug regimen with a dose scheme that is convenient and improves the bioavailability of alendronate.

TABLE 1A (alendronate 0 hours after 1-alpha)

SUMMARY OF ALENDRONATE QUANTITY EXCRETED (µg) IN URINE

Subject #	Period #	Draw Times (Hour)					
		0.000	3.00	6.00	9.00	24.0	total
295	1	BLQ	NRV	6.09	NRV	NRV	6.09
109	1	BLQ	27.33	4.27	BLQ	4.20	35.80
612	1	BLQ	28.01	NRV	NRV	2.91	30.92
648	1	BLQ	40.99	6.90	8.45	7.02	63.36
005	1	BLQ	28.26	8.87	3.52	2.90	43.55
578	1	BLQ	25.29	13.99	2.21	3.68	45.17
						avg=	37.48

BLQ: Below Level of Quantitation NRV: No Reportable Value

TABLE 1B (alendronate 1 hour after 1-alpha)

SUMMARY OF ALENDRONATE QUANTITY EXCRETED (µg) IN URINE

Subject #	Period #	Draw Times (Hour)					
		0.000	3.00	6.00	9.00	24.0	total
295	2	BLQ	42.05	4.71	NRV	7.58	54.34
109	2	BLQ	39.99	4.01	NRV	3.47	47.47
612	2	BLQ	39.73	4.42	4.30	4.58	53.03
648	2	1.61	109.98	9.02	7.51	8.79	136.91
005	2	BLQ	BLQ	BLQ	BLQ	BLQ	0.00
578	2	BLQ	4.87	1.82	NRV	NRV	6.69
						avg=	49.74

BLQ: Below Level of Quantitation NRV: No Reportable Value

TABLE 1C (alendronate 2 hours after 1-alpha)

SUMMARY OF ALENDRONATE QUANTITY EXCRETED (µg) IN URINE

Subject #	Period #	Draw Times (Hour)					
		0.000	3.00	6.00	9.00	24.0	total
295	3	3.14	25.52	NRV	3.82	5.84	38.32
109	3	BLQ	NRV	NRV	2.30	2.97	5.27
612	3	BLQ	NRV	4.11	2.73	4.11	10.95
648	3	BLQ	38.98	20.58	7.32	11.28	78.16
005	3	NRV	BLQ	NRV	NRV	NRV	0.00
578	3	BLQ	16.10	9.63	1.80	NRV	27.53
						avg=	26.71

BLQ: Below Level of Quantitation NRV: No Reportable Value

5

TABLE 1D (alendronate 3 hours after 1-alpha)

SUMMARY OF ALENDRONATE QUANTITY EXCRETED (µg) IN URINE

Subject #	Period #	Draw Times (Hour)					
		0.000	3.00	6.00	9.00	24.0	total
295	4	NRV	59.51	5.68	3.87	3.97	73.03
109	4	BLQ	81.05	7.04	NRV	5.06	93.15
612	4	BLQ	35.52	5.01	NRV	4.12	44.65
648	4	BLQ	47.20	7.05	5.72	NRV	59.97
005	4	BLQ	51.07	11.11	13.24	20.07	95.49
578	4	3.81	85.63	13.41	7.10	6.81	116.76
						avg=	80.51

BLQ: Below Level of Quantitation NRV: No Reportable Value

TABLE 1E (alendronate 6 hours after 1-alpha)

SUMMARY OF ALENDRONATE QUANTITY EXCRETED (µg) IN URINE

Subject #	Period #	Draw Times (Hour)					
		0.000	3.00	6.00	9.00	24.0	total
295	5	BLQ	65.02	31.98	6.03	7.28	110.31
109	5	BLQ	49.30	5.09	2.39	4.64	61.42
612	5	4.10	111.68	10.42	4.61	12.55	143.36
648	5	NRV	68.15	8.78	4.25	5.27	86.45
005	5	4.73	65.30	2.55	6.54	5.56	84.68
578	5	NRV	75.32	11.65	3.71	3.67	94.35
						avg=	96.76

BLQ: Below Level of Quantitation NRV: No Reportable Value

Table 2. Average Total Alendronate Excreted as a Function of the Time Interval Between Alphacalcidol and Alendronate Administrations

Hours between administrations	total alendronate (µg)
0	37.5
1	49.7
2	26.7
3	80.5
6	96.8

Table 3. Average Total Alendronate Excreted as a Function of the Time Interval Between Calcitriol and Alendronate Administrations

Hours between administrations	total alendronate (µg)
0	56.9
1	56.8
2	70.0
3	108.1
6	36.0

EXAMPLE 2: In-Vivo Study on Improving the Bioavailability of Alendronate: Effect of Varying Predose Intervals of Calcitriol in a Combination Drug Regimen with Alendronate.

An *in vivo* study in an animal model was conducted to determine whether calcitriol, administered at varying predose intervals (time intervals) in combination therapy with alendronate increased the bioavailability of alendronate compared with the administration of alendronate alone.

Six female beagle dogs, each approximately 2 years old and weighing approximately 9 kg were the animal models in this study. The same animals were

used in each of five separate treatment sessions lasting 22-24 hours each, the duration of each session depending on the predose test interval being measured. The same drugs at identical dosages were administered in every treatment, *viz.*, calcitriol (ROCALTROL®, 25.0 μg gel capsule; ROCHE) was the Vitamin D_3 derivative administered as the predose drug and alendronate sodium (Fosamax®, 10 mg tablet, Merck, Sharp & Dohme) was the bis-phosphonate administered as the therapeutic drug. There was a 7 day wash-out period between sessions. The clinical state of each dog was checked within 48 hours prior to each treatment session and again after the last session. In each session the animals were dosed in the fasted state (n.p.o. 10-12 hours). The dogs were fed a standardized meal (Shur-Gain, Canada, 200-250 grams) four hours after administration of the therapeutic dose of alendronate.

During each session, the dogs were housed in steel metabolic cages. Urine samples were recovered from the bottom of the metabolic cages. At each collection point, two representative samples of urine (*ca.* 15 ml each) were taken in capped polypropylene vials and immediately frozen at -20° C. The remainder of the sample was frozen and retained.

Urine samples were analyzed for alendronate by HPLC with fluorescence detection (Anapharm, Inc., Quebec, Canada).

In each session, the predose study drug, calcitriol, was administered in the A.M., in the fasted state, with 10-20 ml tap water to facilitate swallowing, followed by hydration with 250 ml tap water (adjusted to pH = 2.0) *via* gastroesophageal tube. During the monitoring (collection) period of each session, dogs were hydrated *via* gastroesophageal tube with 200-250 ml tap water (adjusted to pH = 2.0) on the evening prior to initiation of each testing session and subsequently, with 200-250 ml pH-adjusted tap water every two hours post-administration of the therapeutic dose of alendronate, for up to 10 hours. As noted above, a meal was allowed 4 hours after the administration of alendronate.

In the first (reference) study session, the therapeutic dose of alendronate was administered alone, with hydration by administration of 250 ml pH-adjusted tap water *via* a gastroesophageal tube.

In the second (reference) study session, the predose of calcitriol and the therapeutic dose of alendronate were administered simultaneously, with 10-20 ml tap water to facilitate swallowing, immediately followed by 250 ml pH-adjusted tap water *via* a gastroesophageal tube.

In the third through sixth study sessions, the predose of calcitriol was administered with 10-20 ml tap water. At intervals of 1, 2, 3, or 6 hours, respectively, following the administration of the predose of calcitriol in each of the consecutive study sessions, the therapeutic dose of alendronate was administered with 10-20 ml tap water, immediately followed by 250 ml tap water *via* gastroesophageal tube.

For each calcitriol predose time interval tested, cumulative levels of alendronate concentrations in urine were determined over 12 hours post-administration of the therapeutic alendronate dose at collection time points beginning at the 0 hour prior to alendronate dose and again at 3, 6, 9, and 12 hours following the alendronate dose.

The results of the analyses of alendronate in urine for the five treatments are reported in Table 4. Table 4 collects the average of the total excreted alendronate as a function of the time interval between calcitriol administration and alendronate administration.

The results showed that the total alendronate bioavailability increased considerably 3 hours after the administration of calcitriol. Alendronate bioavailability without the vitamin D derivative in this dog model was about 30 μg to 50 μg. Calcitriol, administered 3 hours before the alendronate administration increased this value to 108 μg. By delaying the release of the calcitriol predose for 3 to 5 hours and waiting for a time interval of several hours before administering the bis-phosphonate, the combination drug regimen is both more effective and more convenient.

Table 4. Average Total Alendronate Excreted as a Function of the Time Interval Between Calcitriol and Alendronate Administrations

Hours between administrations	total alendronate (μg)
0	56.9
1	56.8
2	70.0
3	108.1
6	36.0

EXAMPLE 3: In-Vivo Study on Improving the Bioavailability of Alendronate: Effect of Varying Predoses in a Combination Drug Regimen with Alendronate.

An *in vivo* study in an animal model was conducted to determine whether calcitriol or alphacalcidol, administered in varying predose intervals (time intervals) in combination therapy with alendronate increased the bioavailability of alendronate compared with the administration of alendronate alone.

The method of example 1 was used. This study compared sessions of Fosalan® alone, dosing of Fosalan® with predosing of alphacalcidol at predose intervals of 6 hours, 8 hours, and 10 hours, and dosing of Fosalan® predosing with calcitriol at a predose interval of 3 hours. The results are shown below in Table 5.

Table 5: Cumulative Alendronate in Urine (ugm)

dog #	fosalen alone	Calcitriol 3hr predose	alphacalcidol 6hr predose	alphacalcidol 8hr predose	alphacalcidol 10hr predose
205	48.84	106.68	77.78	110.49	233.93
109	65.52	73.68	44.34	90.85	48.66
612	20.67	51.48	81.69	116.53	86.74
648	83.88	138.12	77.83	95.71	192.41
005	34.06	136.86	104.74	85.29	64.46
578	61.75	222.4	69.57	77.67	12.23
avg	52.5	121.5	76.0	96.1	106.4
median	55.3	121.8	77.8	93.3	75.6
std dev	22.8	60.2	19.5	14.9	87.2

Having thus described the invention with reference to various preferred embodiments, those skilled in the art will appreciate modifications of these exemplary embodiments that do not depart from the spirit and scope of the invention as defined by the claims that follow.

CLAIMS

What is claimed is:

1. A method of increasing the bioavailability of a bis-phosphonate comprising administering an effective predose of a vitamin D derivative, and after a time interval, administering a therapeutic dose of a bis-phosphonate.

2. The method of claim 1, wherein the release of the Vitamin D derivative predose is delayed.

3. The method of any one of claims 1 and 2, wherein said vitamin D derivative is selected from the group consisting of calcitriol, alphacalcidol, 24,25-dihydroxy vitamin D_3, and calcifediol.

4. The method of claim 3, wherein the vitamin D derivative is alphacalcidol.

5. The method of claim 3, wherein the vitamin D derivative is calcitriol.

6. The method of any one of claims 1 and 2, wherein said time interval is about equal to the amount of time required for blood calcium level to reach a maximum after administering the vitamin D derivative.

7. The method of any one of claims 1 and 2, wherein said time interval is at least about 6 hours.

8. The method of claim 6, wherein said time interval is about 6 hours to about 14 hours.

9. The method of any one of claims 1 and 2, wherein the predose of the vitamin D derivative is about 0.1 μg to about 10 μg.

10. The method of any one of claims 1 to 3, wherein said bis-phosphonate is selected from the group consisting of alendronate, risedronate, etidronate, zoledronate, and tiludronate.

11. The method of claim 10, wherein said bis-phosphonate is alendronate.

12. The method of claim 11, wherein the dose of alendronate is about 10 mg to about 70 mg.

13. The method of any one of claims 1 and 2, wherein said predose of vitamin D derivative is administered at bedtime and the dose of bis-phosphonate is administered before eating.

14. The method of any one of claims 1 and 2, wherein the time interval is a period of fasting.

15. The method of claim 2, wherein the delayed-release predose of vitamin D derivative is a dosage form with a delayed-release enteric coating.

16. The method of claim 15, wherein said release of the vitamin D derivative is delayed for at least about 3 hours to about 5 hours.

17. The use of a bis-phosphonate for the manufacture of a medicament for treating osteoporosis, metastatic bone disease, and Paget's disease which comprises administering an effective predose of a vitamin D derivative prior to administering the bis-phosphonate.

18. The use of a vitamin D derivative for the manufacture of a medicament for treating osteoporosis, metastatic bone disease, and Paget's disease which comprises administering a bis-phosphonate after administering the vitamin D derivative.

19. The use of a vitamin D derivative and a bis-phosphonate for the manufacture of a medicament for treating osteoporosis, metastatic bone disease, and Paget's disease which comprises administering the vitamin D derivative and then after a time interval administering the bis-phosphonate.